Translation

PCT/FR2003/002010

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference BLOcp226/107	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/FR2003/002010	International filing date (*day/month/year*) 27 juin 2003 (27.06.2003)	Priority date (*day/month/year*) 28 juin 2002 (28.06.2002)
International Patent Classification (IPC) or national classification and IPC C12N 5/06		
Applicant INSTITUT PASTEUR		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of _____ sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
20 janvier 2004 (20.01.2004)	30 September 2004 (30.09.2004)
Name and mailing address of the IPEA/EP Facsimile No.	Authorized officer Telephone No.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/FR2003/002010

I. Basis of the report

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed

☒ the description:

pages 1-17, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☒ the claims:

pages 1-9, as originally filed
pages _____, as amended (together with any statement under Article 19
pages _____, filed with the demand
pages _____, filed with the letter of _____

☒ the drawings:

pages 1/5-5/5, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☐ the sequence listing part of the description:

pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
☐ the language of publication of the international application (under Rule 48.3(b)).
☐ the language of the translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority in written form.
☐ furnished subsequently to this Authority in computer readable form.
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, sheets/fig _____

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rule 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/FR2003/002010

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1-4, 7 (industrial application)

because:

☒ the said international application, or the said claims Nos. 1-4, 7 (see separate sheet) relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _____ are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos. _____.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: III

Claims 1-4 and 7 relate to methods for the treatment of the human or animal body by surgery. As a result, no opinion will be established with respect to the industrial applicability of the subject matter of these claims (PCT Rule 67.1(iv)).

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	2, 5	YES
	Claims	1, 3, 4, 6-9	NO
Inventive step (IS)	Claims		YES
	Claims	1-9	NO
Industrial applicability (IA)	Claims	5, 6	YES
	Claims		NO

2. Citations and explanations

The present report mentions the following documents cited in the search report:

D1: DIMARIO JOSEPH X ET AL: "Differences in the developmental fate of cultured and noncultured myoblasts when transplanted into embryonic limbs" EXPERIMENTAL CELL RESEARCH, vol. 216, no. 2, 1995, pages 431-442, XP002264234 ISSN: 0014-4827;

D2: WO 01 36482 A (MIGNONE JOHN; COLD SPRING HARBOR LAB (US); ENIKOLOPOV GRIGORI N (US)) 25 May 2001 (2001-05-25) (cited in the application);

D3: POUZET BRUNO ET AL: "Intramyocardial transplantation of autologous myoblasts: Can tissue processing be optimized?" CIRCULATION, vol. 102, no. 19 Supplement, 7 November 2000 (2000-11-07), pages III.210-III.215, XP002264235 ISSN: 0009-7322.

Novelty (PCT Article 33(2))

The subject matter of claims 1, 3, 4 and 6-9 lacks novelty

over documents **D1, D2 and D3:**

D1 describes a method for transplanting chicken or quail myoblasts of embryonic, foetal or adult origin into limb buds of chicken embryos. According to said method, the muscle areas are first chopped, then exposed to enzymatic digestion (collagenase and trypsin). The freshly isolated myoblasts are transplanted directly. Unlike the fibroblasts that are cultured prior to transplantation, said myoblasts are capable of forming numerous muscle fibres with long-term persistence (D1, the abstract; page 432, column 1, paragraph 1 to column 2, paragraph 2; page 440, last paragraph to page 441, last paragraph).

The stem cells or cell compositions produced using the method described in D1, as well as the transplantation method described in D1, are prejudicial to the novelty of claims 6-9.

D2 describes a method for transplanting neural stem cells, in which the cells are not precultured. (Mouse) brain tissue is placed in a specific medium (DMEM/F12) and dissociated, firstly by adding trypsin then by using mechanical means (pipette). The cells are collected by means of centrifugation, then stored in Hank's Buffered Salt Solution (HBSS) before being injected into a rat brain. After one week, it was possible to note the survival of the cells and their incorporation into the brain (D2, page 1, lines 12-26; page 21, lines 22-27; example 8). D2 discloses all of the steps of the method of claim 1 and is, as a result, prejudicial to the novelty of claims 1, 3 and 4. The stem cells or cell compositions as well as the transplantation method disclosed in D2 deprive claims 6-9 of novelty.

D3 also discloses a method for preparing skeletal myoblasts, in which the muscle tissue is chopped then exposed to enzymatic dissociation. The cells are collected by means of sedimentation and centrifugation, then kept in a specific culture medium consisting of F12 with 20% of FBS added thereto, and containing basic fibroblast growth factor (bFGF) (D2, page III-211, "Cell culture methodology", column 1, last paragraph to column 2, line 4). The Examining Authority considers that the cell composition and the stem cells produced in D3 deprive claims 6, 8 and 9 of novelty.

Inventiveness (PCT Article 33(3))

1. The subject matter of claims 2 and 5 does not involve an inventive step in view of D1 or D2, for the following reasons:

D1 and D2 describe the production of muscle or neural stem cells and the transplantation of same into an animal without carrying out a preculture step. Even though D1 or D2 do not explicitly define a specific medium for preserving the cells before carrying out the transplantation step, defining the properties of such a medium is within the abilities of a person skilled in the art. It follows that the method as per claim 2 is not considered to be inventive.

Furthermore, D1 and D2 disclose stem cells such as the ones claimed in the present application (see above) and mention the therapeutic use of stem cells in general (D1, page 441, last paragraph; D2, page 6, line 31). As a result, the therapeutic use of

the stem cells produced in D1 or D2 would be obvious to a person skilled in the art and does not involve an inventive step.

2. It is brought to the applicant's attention that, in so far as the subject matter of the claims relates specifically to the grafting of skeletal muscle cells to the myocardium without any pre-expansion of said cells in *in-vitro* culture, said subject matter is considered to be novel and inventive in relation to the documents cited in the international search report.